

# Simple Integer Risk Score to Determine Prognosis of Patients With Hypertension and Chronic Stable Coronary Artery Disease

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**Background**—It is difficult to accurately determine prognosis of patients with hypertension and chronic stable coronary artery disease (CAD). Our aim was to construct a risk score for predicting important adverse events in this population.

**Methods and Results**—Patients with hypertension and chronic stable CAD enrolled in the International Verapamil-SR/Trandolapril Study (INVEST) comprised the study cohort. Candidate predictor variables were obtained from patients with at least 1 postbaseline visit. Patients were divided into development (n=18 484) and validation cohorts (n=2054). Cox regression model identified predictors of the primary outcome: all-cause mortality, myocardial infarction, or stroke at a mean follow-up of 2.3 years. The hazard ratio of each variable was rounded to the nearest integer to construct score weights. A score 0 to 4 defined low-risk, 5 to 6 intermediate-risk and  $\geq 7$  high-risk. The following variables were retained in the final model: age, residence, body mass index, on-treatment heart rate and BP, prior myocardial infarction, heart failure, stroke/transient ischemic attack, smoking, diabetes, peripheral arterial disease, and chronic kidney disease. The primary outcome occurred in 2.9% of the low-risk group, 6.5% of the intermediate-risk group, and 18.0% of the high-risk group ( $P$  for trend  $<0.0001$ ). The model was good at discriminating those who had an event versus those who did not (C-statistic=0.75). The model performed well in a validation cohort (C-statistic=0.77).

**Conclusion**—Readily available clinical variables can rapidly stratify patients with hypertension and chronic stable CAD into useful risk categories. (*J Am Heart Assoc.* 2013;2:e000205 doi: 10.1161/JAHA.113.000205)

**Key Words:** clinical decision rule • coronary artery disease • coronary heart disease • ischemic heart disease • prognosis • risk score

One mechanism to improve the quality and cost of health care delivery is to categorize patients into risk categories whereby the level of care would be targeted to the risk profile of a particular patient.<sup>1</sup> For coronary artery disease (CAD), expensive medications and procedures are commonly used; however, relatively little attention has been devoted to targeting such therapies to the overall risk of the patient. During a patient's lifetime, a significant proportion of health care delivery will take place on an outpatient level. CAD patients are often considered "high-risk" by limited characteristics such as diabetes status, but this may not provide an accurate determination of the patient's overall risk profile and

response to certain treatments.<sup>2</sup> Therefore, a simple means to risk stratify chronic stable CAD patients with readily available clinical information is needed.

A risk score (clinical decision rule) aggregates various patient characteristics into a numerical score that can be useful in estimating prognosis.<sup>3–6</sup> Numerous risk scores have been developed to risk stratify patients at the time of an acute coronary syndrome.<sup>7–10</sup> Unfortunately, these decision rules do not apply to the larger group of ambulatory patients with chronic stable CAD. Therefore, our objective was to construct and internally validate a simple-to-use risk score using readily available clinical data to predict future adverse events among patients with hypertension and chronic stable CAD.

## Methods

### Study Protocol

Details regarding the International Verapamil-SR/Trandolapril Study (INVEST) protocol and outcomes have been published elsewhere.<sup>11,12</sup> Briefly, INVEST was an international randomized trial that compared the effects of a calcium antagonist

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Received April 15, 2013; accepted July 26, 2013.

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(verapamil SR)-based strategy with a  $\beta$ -blocker (atenolol)-based strategy for treatment of hypertension among 22 576 patients  $\geq 50$  years of age with clinically stable CAD. Since there was no difference between treatment strategies, the entire INVEST cohort was considered in the construction of this risk score.<sup>4</sup> CAD was defined as prior myocardial infarction, abnormal coronary angiogram ( $\geq 50\%$  stenosis of at least 1 major epicardial vessel), concordant abnormalities on 2 different types of cardiac tests (eg, electrocardiogram, echocardiogram, or myocardial perfusion study), or classic angina pectoris. The following patients were excluded: unstable angina, coronary revascularization or stroke within the last month, myocardial infarction within the last 3 months,  $\beta$ -blocker use within the last 2 weeks or within 12 months of a myocardial infarction, sinus bradycardia, sick sinus syndrome or type 2 or 3 heart block without permanent pacemaker, Wolf-Parkinson-White, ventricular tachycardia or other serious arrhythmias, severe heart failure (New York Heart Association class IV), severe renal dysfunction (creatinine  $\geq 4.0$  mg/dL), hepatic dysfunction, contraindication to study medication, or life expectancy  $< 2$  years. Enrollment began September 1997 and follow-up was completed in February 2003. The study was conducted according to the principles of the Declaration of Helsinki. Local institutional review boards and ethics committees approved the protocol and written informed consent was obtained from all subjects.

Patient characteristics were recorded by the physician investigator at baseline (visit 1). Coronary angioplasty represented mostly percutaneous coronary intervention with bare-metal stents. Type of arrhythmia was not recorded; however, due to the age of participants and exclusions for serious arrhythmias, this mostly represented atrial fibrillation and/or flutter. Although peripheral vascular disease was recorded, we preferred to report this condition with the more contemporary term, peripheral arterial disease.<sup>13</sup>

Protocol scheduled follow-up visits occurred every 6 weeks for the first 6 months (visits 2 to 5), then twice per year until 2 years after the last patient was enrolled. Blood pressure (BP) was recorded as the mean of 2 cuff BP measurements after the patient was sitting comfortably for at least 5 minutes. Target BP was  $< 140/90$  mm Hg, or  $< 130/85$  mm Hg if diabetes or chronic kidney disease was present.<sup>14</sup> Trandolapril and hydrochlorothiazide could also be added as necessary to achieve target BP. Titration of study medications was mostly complete by the 6-month visit.

The primary study outcome was the first occurrence of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke. Outcomes were adjudicated by a blinded events committee by review of pertinent patient and hospital records. Nonfatal myocardial infarction was defined as an elevation in cardiac enzymes (troponin I or T, or

creatinine-kinase myocardial band isoenzyme) greater than the upper limit of normal with ischemic symptoms and/or ischemic electrocardiographic changes. Nonfatal stroke was defined as a sudden onset of a neurological deficit that persisted for at least 24 hours and confirmed by neurological imaging or neurology consult.

## Statistical Methods: Risk Score Construction and Validation

Patients who had at least 1 postbaseline visit were landmarked for analysis. To reflect a period of stable BP, the 6-month visit was preferentially used; however, in the absence of 6-month data, any postbaseline visit between 6 weeks and 6 months was included, with preference given to the available visit closest to 6 months ( $n=20\,537$ ). Ninety percent of this cohort was randomly selected as a development cohort, while the remaining 10% was utilized as an internal validation cohort.

Our goal was to select dichotomous or categorical variables that could be readily identified during a routine office visit. Age was categorized as  $< 65$  years (referent), 65 to 74 years, or  $\geq 75$  years. Residence was categorized as North America or non-North America (Europe, Mexico, or Caribbean [referent]). On-treatment BP was categorized as  $< 110$  mm Hg,<sup>15,16</sup> 110 to 139 mm Hg (referent), or  $\geq 140$  mm Hg.<sup>17,18</sup> Heart rate was categorized as  $< 85$  beats per minute (referent) or  $\geq 85$  beats per minute.<sup>19,20</sup> Body weight was categorized as a body mass index (BMI)  $< 20$  kg/m<sup>2</sup>, 20 to 24.9 kg/m<sup>2</sup>, 25 to 29.9 kg/m<sup>2</sup>, versus  $\geq 30$  kg/m<sup>2</sup> (referent).<sup>21–23</sup> Categorization was justified due to lack of linearity of the predictor variables on the primary outcome. The referent category was assigned so that association between the predictor variables and the primary outcome was positive.

A Cox regression model tested each candidate variable predictor of the primary outcome (all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke). An initial model forced all candidate variables into it as a full model, while more restrictive models were formed at a 5% and 1% significance level using backward elimination. An additional model only considered nonmodifiable variables. The  $\beta$  coefficients and standard errors in each multivariable Cox regression models are presented. Hazard ratios were calculated by taking the exponentials of the  $\beta$  coefficients. Hazard ratios of covariates were rounded to the nearest integer to construct score weights. The range of possible total score weights was divided into approximately equal groups to stratify patients into low-, intermediate-, and high-risk tertiles. Model discrimination was determined by calculating the C-statistic, which is the area under the receiver operator curve.<sup>24</sup> Model calibration was evaluated by the Hosmer-Lemeshow goodness-of-fit test

statistic, where the expected incidence of the primary outcome from the development cohort was compared against the observed incidence from the validation cohort.<sup>25</sup> Baseline characteristics were reported as frequencies, and continuous and categorical variables were compared with Student's *t* test and the  $\chi^2$  test, respectively. A *P* value <0.05 was considered significant. Analyses were performed with SAS software 9.2 (SAS Institute, Inc). No funding was obtained for the conduct of this study.

## Results

The characteristics of the development cohort (n=18 484) and internal validation cohort (n=2054) were similar at the time of the landmark except for arrhythmia, which was slightly more common in the development cohort (Table 1). Mean heart rate and BP was 71 beats per minute and 134/78 mm Hg, respectively. From the landmark until the end of follow-up (mean=2.3 years), 1348 (7.3%) patients died, 262 (1.4%) had a nonfatal myocardial infarction, and 231 (1.3%) had a nonfatal stroke.

The proportion of patients correctly classified as having a systolic BP <110 and  $\geq$ 140 mm Hg during a one-time office visit was compared against the mean BP from the landmark to the end of follow-up. The sensitivity and specificity of an office visit BP <110 mm Hg was 70% and 97%, respectively, while the sensitivity and specificity of an office visit BP  $\geq$ 140 was 72% and 83%, respectively.

Table 2 displays the full model and more restrictive models constructed at the 5% and 1% significance levels. Since the 1% significance level was the most parsimonious model and retained good discrimination (C-statistic=0.75), this was the model the risk score was built upon. We additionally explored a model where age, BMI, heart rate, and systolic BP were considered as continuous variables; however, this had the same discrimination as the categorical model. We also compared gender-specific models with a gender-pooled model and found no evidence for effect modification by gender. Table 3 displays the score weights assigned to each retained predictor variable. The total possible score was 21 points; however, no patient had a score >18. The absolute event rate for each total point score is provided in a score sheet in Table 4. The frequency of distribution of risk scores is displayed in Figure 1. A score of 0 to 4 defined low-risk, 5 to 6 defined intermediate-risk, and  $\geq$ 7 defined high-risk.

The incidence of adverse events was 2.9% in the low-risk group, 6.5% in the intermediate-risk group, and 18.0% in the high-risk group (Figure 1). The incidence of adverse events in the validation cohort was similarly increased in a stepwise fashion (*P* for trend <0.0001; C-statistic=0.77). The Hosmer-Lemeshow goodness-of-fit test statistic was 8.03

(*P*=0.43). Frequencies of individual cardiovascular outcomes are listed in Table 5.

Figure 2 displays the risk for an adverse event according to different eligibility criteria: any prior myocardial infarction, known coronary stenosis or ischemia on 2 different cardiac tests, or only classic angina pectoris. The C-statistics for these sub-groups were 0.74, 0.76, and 0.83 for the 3 groups, respectively. The Hosmer-Lemeshow goodness-of-fit test statistics were 4.3 (*P*=0.83), 7.7 (*P*=0.46), and 7.4 (*P*=0.49), respectively.

## Discussion

Our study constructed and internally validated a simple-to-use integer risk score to predict future adverse events from a large international database of patients with hypertension and chronic stable CAD. This allowed us to stratify patients into low-, intermediate-, and high-risk categories. Adverse outcomes were primarily attributable to deaths. Strength of the current analysis is that all of the predictors are readily available during a routine clinic visit. The risk score had good discriminative ability in determining which patients would suffer from an adverse event and provided similar predictive accuracy among different study eligibility criteria (ie, prior myocardial infarction versus only classic angina pectoris). Such information might be useful to select high-risk patients for closer surveillance, more aggressive risk factor modification, and performance of diagnostic/therapeutic procedures, while being more conservative in low-risk patients; however, these concepts would need to be prospectively tested. Model performance was slightly improved when comparing a model with nonmodifiable factors (C-statistic=0.74) to models with modifiable factors (C-statistic=0.75). This could signal the importance of weight, heart rate, and BP control among these patients.

We analyzed patients who had at least 1 postbaseline visit, and preferentially used the 6-month visit when titration of antihypertensive medications was mostly complete. Accordingly, these results are generalizable to ambulatory patients with chronic stable CAD who are on a stable antihypertensive regimen. We decided to perform a landmark analysis for several reasons. The mean BP in INVEST was significantly reduced after study medications were initiated. This mirrors clinical practice where patients with hypertension will undergo a dedicated attempt by their practitioner to reach target BP through titration of antihypertensive medications. In lieu of mean BP which would not be readily available in clinical practice, we used a carefully measured value during 1 office visit. This correlated well with mean BP and had good or very good specificity. Patients who have a one-time BP value within the referent range (110 to 139 mm Hg), but close to the

**Table 1.** Patient Characteristics at the Time of the Landmark

Characteristic	Development Cohort, n=18 484	Validation Cohort, n=2054	P Value
Age, y, mean (SD)	66.0 (9.7)	66.1 (9.8)	0.76
<65 years, %	45.8	45.5	—
65 to 74 years, %	33.1	33.1	—
≥75 years, %	21.1	21.5	—
Women, %	52.1	51.1	0.38
Nonwhite race, %	48.5	49.0	0.67
Global region:			
North America	77.0	79.8	0.09*
European	6.8	5.9	—
Mexico/Caribbean	16.0	14.2	—
BMI, kg/m <sup>2</sup> , mean (SD)	29.2 (6.8)	29.4 (10.4)	0.35
<20 kg/m <sup>2</sup> , %	2.2	2.4	—
20 to 24.9 kg/m <sup>2</sup> , %	19.8	19.6	—
25 to 29.9 kg/m <sup>2</sup> , %	40.2	39.4	—
≥30 kg/m <sup>2</sup> , %	37.9	38.6	—
HR, beats/minute, mean (SD)	71.3 (9.5)	71.4 (9.5)	0.48
≥85 beats/minute, %	7.1	7.3	—
SBP, mm Hg, mean (SD)	134.4 (17.2)	134.1 (17.3)	0.54
SBP <110 mm Hg, %	3.0	3.3	—
SBP ≥140 mm Hg, %	32.2	31.1	—
DBP, mm Hg, mean (SD)	78.4 (9.6)	78.3 (9.8)	0.60
History of, %			
Myocardial infarction	32.2	32.3	0.89
Unstable angina	11.5	11.0	0.48
Classic angina pectoris	68.0	67.2	0.45
Coronary revascularization <sup>†</sup>	27.3	27.4	0.96
Heart failure (class I to III)	5.7	5.4	0.55
Arrhythmia <sup>‡</sup>	7.2	5.9	0.03
Stroke/transient ischemic attack	7.6	7.1	0.41
Smoking <sup>§</sup>	46.5	46.1	0.73
Diabetes mellitus <sup>  </sup>	29.9	30.5	0.53
Hyperlipidemia <sup>¶</sup>	56.2	55.8	0.70
Peripheral arterial disease	12.0	11.5	0.59
Chronic kidney disease	1.9	1.8	0.64
Medications, %			
Aspirin	58.1	56.0	0.06
NSAID	16.8	17.0	0.75
Lipid lowering agent	37.5	36.2	0.27
Nitrate	32.5	31.0	0.15

BMI indicates body mass index; DBP, diastolic blood pressure; HR, heart rate; kg, kilogram; m, meter; NSAID, non-steroidal anti-inflammatory drug; SBP, systolic blood pressure; SD, standard deviation.

\*P value across categories.

<sup>†</sup>Includes coronary artery bypass grafting and percutaneous coronary intervention.

<sup>‡</sup>Type of arrhythmia not recorded, but mostly represented atrial fibrillation.

<sup>§</sup>Includes current and past smoking.

<sup>||</sup>Defined as diagnosis of diabetes or use of oral hypoglycemic medications and/or insulin.

<sup>¶</sup>Defined as diagnosis of hypercholesterolemia or use of lipid lowering medications.

**Table 2.** Predictors of All-Cause Mortality, Non-Fatal Myocardial Infarction, or Non-Fatal Stroke

Predictor	Full Model	Non-Modifiable Factors	5% Significance Model	1% Significance Model
65 to 74 years of age	0.44 (0.06)*	0.47 (0.06)*	0.45 (0.06)*	0.44 (0.06)*
≥75 years of age	0.99 (0.06)	1.08 (0.06)	1.0 (0.06)	1.0 (0.06)
Male gender	0.11 (0.05)	0.08 (0.05)	0.13 (0.05)	
North American residence	0.56 (0.08)	0.56 (0.08)	0.55 (0.08)	0.55 (0.08)
Nonwhite race	0.02 (0.05)	0.03 (0.05)		
BMI <20 kg/m <sup>2</sup>	0.89 (0.12)		0.89 (0.12)	0.86 (0.12)
BMI 20 to 24.9 kg/m <sup>2</sup>	0.37 (0.07)		0.37 (0.07)	0.37 (0.07)
BMI 25 to 29.9 kg/m <sup>2</sup>	0.13 (0.06)		0.13 (0.06)	0.14 (0.06)
Heart rate ≥85 beats/minute	0.26 (0.08)		0.25 (0.08)	0.24 (0.08)
SBP <110 mm Hg	0.43 (0.12)		0.43 (0.12)	0.43 (0.12)
SBP ≥140 mm Hg	0.11 (0.05)		0.11 (0.05)	0.10 (0.05)
History of:				
Myocardial infarction	0.35 (0.05)	0.36 (0.05)	0.38 (0.05)	0.39 (0.05)
Unstable angina	0.04 (0.07)	0.04 (0.07)		
Classic angina pectoris	−0.06 (0.05)	−0.06 (0.05)		
Coronary revascularization	0.06 (0.06)	0.05 (0.06)		
Heart failure	0.62 (0.07)	0.66 (0.07)	0.66 (0.07)	0.65 (0.07)
Arrhythmia	0.10 (0.08)	0.11 (0.08)		
Stroke/TIA	0.56 (0.07)	0.57 (0.07)	0.55 (0.07)	0.55 (0.06)
Smoking	0.31 (0.05)	0.33 (0.05)	0.32 (0.05)	0.35 (0.05)
Diabetes mellitus	0.54 (0.05)	0.49 (0.05)	0.55 (0.05)	0.55 (0.05)
Peripheral arterial disease	0.17 (0.06)	0.17 (0.06)	0.18 (0.06)	0.18 (0.06)
Chronic kidney disease	0.45 (0.11)	0.46 (0.11)	0.46 (0.11)	0.48 (0.11)
Left ventricular hypertrophy	0.08 (0.06)	0.07 (0.06)		
Medication use:				
Calcium channel-blocker strategy	−0.05 (0.04)			
Aspirin	−0.005 (0.05)			
Lipid lowering therapy	−0.05 (0.06)			
C-statistic	0.75	0.74	0.75	0.75

Referent age is <65 years, referent BMI is ≥30 kg/m<sup>2</sup>, referent heart rate is <85 beats/minute, and referent SBP is 110 to 139 mm Hg. BMI indicates body mass index; CI, confidence interval; kg, kilogram; m, meter; SBP, systolic blood pressure; TIA, transient ischemic attack.

\*Estimated  $\beta$  coefficients (standard error) for 4 Cox regression models adjusting for all the other variables in the model. The hazard ratios can be calculated by taking the exponential of the  $\beta$  coefficients.

lower/upper threshold may need additional BP readings or even ambulatory BP monitoring to accurately classify them.

Most of the predictors in this risk score have been well documented to increase the hazard for adverse events: advanced age,<sup>22,26</sup> elevated BP,<sup>26</sup> congestive heart failure,<sup>22,27</sup> stroke,<sup>26</sup> diabetes,<sup>22,26,28,29</sup> chronic kidney disease,<sup>26,28,30,31</sup> myocardial infarction,<sup>22,26,28</sup> smoking,<sup>22,26</sup> and peripheral arterial disease.<sup>13,32</sup> However, the aggregated effect of multiple risk factors among chronic stable CAD patient is less well known.<sup>26,33</sup>

Accumulating evidence is challenging the paradigm that very low BP is superior to a less stringent target for high-risk patients. The ACCORD BP (Action to Control Cardiovascular Risk in Diabetes—Blood—Pressure-lowering arm) trial randomized diabetic patients to a goal systolic BP <120 mm Hg (mean 119 mm Hg) compared with a goal <140 mm Hg (134 mm Hg).<sup>34</sup> At 4.7 years of follow-up, cardiovascular outcomes were similar in the 2 groups. An observational study conducted among diabetic patients with hypertension and stable CAD, documented similar outcomes with an achieved



**Table 3.** Score Weights Assigned to Predictor Variables in the Development of the INVEST Risk Score

Characteristic	Univariate Model		Multivariate Model		Score Weight
	HR (95% CI)	P Value	HR (95% CI)	P Value	
65 to 74 years of age	1.73 (1.53 to 1.95)	<0.0001	1.56 (1.38 to 1.76)	<0.0001	2
≥75 years of age	3.31 (2.95 to 3.72)	<0.0001	2.71 (2.39 to 3.07)	<0.0001	3
Male gender	1.22 (1.11 to 1.33)	<0.0001			
North American residence	1.97 (1.69 to 2.29)	<0.0001	1.73 (1.48 to 2.03)	<0.0001	2
Nonwhite race	0.77 (0.70 to 0.85)	<0.0001			
BMI <20 kg/m <sup>2</sup>	3.07 (2.46 to 3.84)	<0.0001	2.38 (1.89 to 2.98)	<0.0001	2
BMI 20 to 24.9 kg/m <sup>2</sup>	1.64 (1.44 to 1.85)	<0.0001	1.46 (1.28 to 1.66)	<0.0001	1
BMI 25 to 29.9 kg/m <sup>2</sup>	1.21 (1.08 to 1.35)	0.001	1.15 (1.02 to 1.29)	0.019	1
Heart rate ≥85 beats/minute	1.40 (1.19 to 1.63)	<0.0001	1.27 (1.09 to 1.49)	0.0046	1
SBP <110 mm Hg	1.80 (1.44 to 2.25)	<0.0001	1.54 (1.22 to 1.93)	0.0001	2
SBP ≥140 mm Hg	1.28 (1.16 to 1.41)	<0.0001	1.11 (1.00 to 1.22)	0.043	1
History of:					
Myocardial infarction	1.73 (1.58 to 1.90)	<0.0001	1.48 (1.35 to 1.63)	<0.0001	1
Unstable angina	1.08 (0.94 to 1.24)	0.27			
Classic angina pectoris	0.71 (0.65 to 0.78)	<0.0001			
Coronary revascularization	1.42 (1.29 to 1.56)	<0.0001			
Heart failure	2.79 (2.44 to 3.20)	<0.0001	1.92 (1.66 to 2.20)	<0.0001	2
Arrhythmia	1.57 (1.35 to 1.82)	<0.0001			
Stroke/TIA	2.59 (2.29 to 2.93)	<0.0001	1.74 (1.53 to 1.97)	<0.0001	2
Smoking	1.42 (1.30 to 1.56)	<0.0001	1.42 (1.29 to 1.57)	<0.0001	1
Diabetes mellitus	1.77 (1.61 to 1.94)	<0.0001	1.73 (1.57 to 1.90)	<0.0001	2
Peripheral arterial disease	1.79 (1.59 to 2.01)	<0.0001	1.20 (1.06 to 1.36)	0.0037	1
Chronic kidney disease	2.94 (2.38 to 3.62)	<0.0001	1.62 (1.30 to 2.01)	<0.0001	2
Left ventricular hypertrophy	1.22 (1.10 to 1.37)	0.0003			
Medication use:					
Calcium channel-blocker strategy	0.97 (0.88 to 1.06)	0.45			
Aspirin	1.18 (1.07 to 1.30)	0.0008			
Lipid lowering therapy	0.97 (0.87 to 1.06)	0.49			
Total possible score					21

Referent age is <65 years, referent BMI is ≥30 kg/m<sup>2</sup>, referent heart rate is <85 beats/minute, and referent SBP is 110 to 139 mm Hg. BMI indicates body mass index; CI, confidence interval; kg, kilogram; HR, hazard ratio; m, meter; PAD, peripheral arterial disease; SBP, systolic blood pressure; TIA, transient ischemic attack.

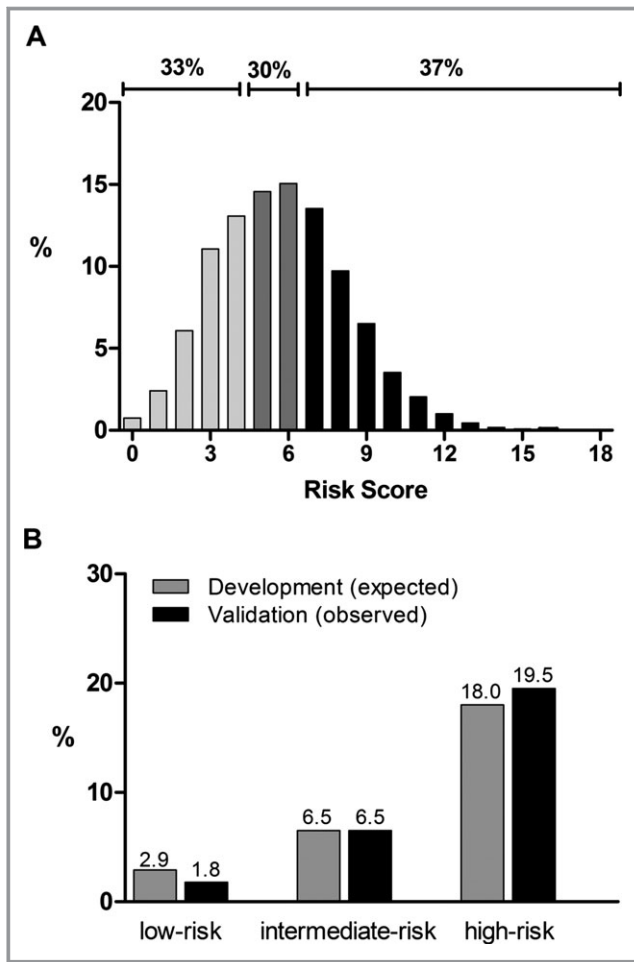
systolic BP <130 mm Hg compared with 130 to <140 mm Hg.<sup>16</sup> More concerning was the group of patients who achieved a systolic BP <110 mm Hg in which case

all-cause mortality was increased. Lastly, a post-hoc analysis from an acute coronary syndrome trial in which half of the patients had hypertension, documented increased adverse

**Table 4.** Score Sheet for Each Total Point Score

Risk Group	Low					Intermediate		High					
Total point score	0	1	2	3	4	5	6	7	8	9	10	11	≥12
Primary outcome, %	0.7	1	2	3	4	5	8	12	16	20	25	30	≥36

Primary outcome estimates were derived from the development cohort. Note, the score sheet was truncated at a score of 12 since risk estimation becomes somewhat unstable beyond that point.



**Figure 1.** A, Frequency of risk scores from the development cohort. Brackets indicate proportion of patients in low-risk (0 to 4), intermediate-risk (5 to 6), and high-risk groups (≥7). B, Frequency of the primary outcome at a mean of 2.3 years according to risk groups. *P* for trend <0.0001 for both the development (C-statistic=0.75) and validation cohorts (C-statistic=0.77).

events among the group with mean systolic BP <110 mm Hg.<sup>15</sup> Writing committees might need to consider an optimal BP range, rather than advocating a “lower is better” approach. Current secondary prevention guidelines

recommend treating BP to a target <140/90 mm Hg or even lower among patients with CAD.<sup>18,35</sup>

In otherwise healthy individuals (ie, no end-organ disease), obesity significantly shortens one’s lifespan.<sup>36</sup> Above a BMI of 25 kg/m<sup>2</sup>, every 5 kg/m<sup>2</sup> increase in BMI is associated with a 30% increase in mortality.<sup>36</sup> However, once CAD (or other end-organ disease) is established, the association between obesity and adverse outcomes becomes complex.<sup>37</sup> This obesity paradox has been well-described and is supported by the current study.<sup>21–23</sup> The mechanism for this paradox is unknown; however, central obesity (ie, waist-to-hip ratio or waist circumference) appears to better predict adverse outcomes than BMI.<sup>38,39</sup> Unfortunately, measurements of central obesity were not obtained in INVEST.

## Limitations

Patients enrolled in a clinical study can be highly motivated and might differ from the general population with CAD. Another limitation, which is due to the study period, is that study participants may not represent contemporary practice. For example, drug-eluting stents were not used during percutaneous coronary intervention and lipid lowering therapy mostly predated the use of high-dose statin therapy.<sup>40</sup>

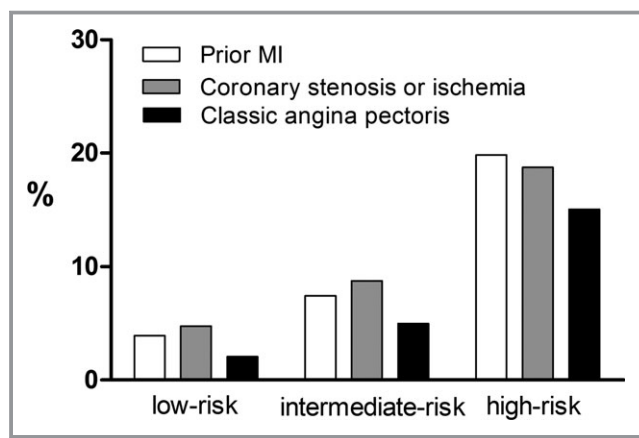
Aspirin use was expected to reduce adverse outcomes<sup>22,33,41</sup>; however, this was not the case in our analysis. Studies support the notion that CAD patients treated with aspirin are higher-risk than CAD patients not treated with aspirin, thus resulting in confounding by indication.<sup>42</sup> Chronic kidney disease, hyperlipidemia, and heart failure were based on physician diagnosis and patient medical records. Had serum creatinine, estimated glomerular filtration rate, lipid profile, and left ventricular ejection fraction been available, the prevalence of these conditions might have been expanded, which could have altered the risk model. Lastly, there were relatively few adverse events attributable to nonfatal myocardial infarction or stroke. Although the reason for this is unknown, the ACCORD trial similarly had a low

**Table 5.** Incidence of Individual Cardiovascular Outcomes

Incidence, %	Low-Risk Group		Intermediate-Risk Group		High-Risk Group	
	Development	Validation	Development	Validation	Development	Validation
All-cause mortality*	1.9	1.5	4.8	4.0	14.2	15.1
CV mortality	1.0	1.1	2.4	1.6	6.6	8.2
Non-CV mortality	0.5	0.6	1.9	2.1	5.9	5.9
Nonfatal MI	0.8	0.2	1.1	0.7	2.3	2.4
Nonfatal stroke	0.3	0.2	0.9	1.8	2.4	3.1

CV indicates cardiovascular; MI, myocardial infarction.

\*A small percentage of mortality was adjudicated as “death confirmation” only, and was not included either in CV mortality or non-CV mortality.



**Figure 2.** Risk for adverse events according to risk groups within different eligibility criteria: any prior myocardial infarction (32% of cohort), known coronary stenosis or ischemia on 2 different cardiac tests (21% of cohort), or only classic angina pectoris (47% of cohort).

frequency of these events despite enrolling high-risk diabetic patients.<sup>43</sup>

## Conclusions

In conclusion, readily available clinical variables can be aggregated into a simple-to-use integer risk score to quantify the risk of future adverse events among patients with treated hypertension and chronic stable CAD. This risk score can be used to stratify CAD patients into low-, intermediate-, and high-risk categories. Ultimately, this risk score could be incorporated into the electronic medical record to assist in health care decisions.

## Sources of Funding

INVEST was funded by a grant from BASF Pharma, Ludwigshafen, Germany; Abbott Laboratories, Abbott Park, IL, USA; and the University of Florida Research Foundation and Opportunity Fund. BASF Pharma and Abbott Laboratories had no role in the design or conduct of the study, collection or analysis of data, or preparation or approval of the manuscript.

## Disclosures

Dr Bavry reported receiving research support from Novartis Pharmaceuticals and Eli Lilly, serving as contractor for Boehringer Ingelheim and the American College of Cardiology's CardioSource. Dr Kumbhani reported receiving consulting fees/honoraria from SomahLutions, Inc, and honoraria from American College of Cardiology. Dr Cooper-DeHoff currently receives funding from the National Heart, Lung and Blood Institute (NHLBI K23 HL086558). Dr Handberg reported

receiving grant support from NHLBI, Abbott Laboratories, Fujisawa, Pfizer, GlaxoSmithKline, and educational grants from the Vascular Biology Working Group (AstraZeneca, Sanofi Aventis, Schering-Plough, Daiichi Sankyo Lilly, AtCor Medical, XOMA). Dr Pepine reported receiving research grants from the NHLBI, Abbott Laboratories, Baxter, Pfizer, Glaxo-SmithKline, and Bioheart Inc; serving as consultant for Abbott Laboratories, Forest Laboratories, Novartis/Cleveland Clinic, NicOx, Angioblast, Sanofi-Aventis, NHLBI, NIH, Medtelligence, and SLACK Inc; receiving unrestricted educational grants from AstraZeneca, AtCor Medical Inc, Daiichi Sankyo Inc, Eli Lilly, Pfizer Inc, Sanofi-Aventis, and Schering-Plough. Dr Pepine receives support in part from the NIH/NCRR Clinical and Translational Science Award to the University of Florida UL1 TR000064. Dr Gong reported that she has no financial disclosures.

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